



**UNIVERSITI PUTRA MALAYSIA**

***SPATIOTEMPORAL TRENDS AND RISK FACTORS OF  
UNSUCCESSFUL TREATMENT OUTCOMES AMONG  
TUBERCULOSIS PATIENTS IN SELANGOR, MALAYSIA***

**KAUR KIRANDEEP KULWANT**

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By

**KAUR KIRANDEEP KULWANT**

**Thesis Submitted to the School of Graduate Studies, Universiti  
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of Doctor of Philosophy**

**August 2021**

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

**SPATIOTEMPORAL TRENDS AND RISK FACTORS OF UNSUCCESSFUL TREATMENT OUTCOMES AMONG TUBERCULOSIS PATIENTS IN SELANGOR, MALAYSIA**

By

**KAUR KIRANDEEP KULWANT**

**August 2021**

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**Faculty : Medicine and Health Sciences**

Tuberculosis (TB) remains the leading cause of mortality among the infectious diseases in Selangor, Malaysia. To identify the spatio-temporal trends and risk factors of unsuccessful treatment outcomes and determine the predictors and time to unsuccessful treatment outcomes in Selangor, Malaysia. Phase I was a retrospective cohort in Selangor (2014-2017) where 18136 respondents from TB registry were selected and their data was recorded using standardized data collection forms and then analyzed using SPSS version 25.0 (multiple logistic regression) to identify the risk factors of unsuccessful treatment outcomes (death, loss to follow-up, failure and not evaluated) and ArcGIS version 10.4 (Global Moran's I and Getis and Ord (Gi\*) statistics) to analyze the spatial distribution, spatio-temporal clustering and develop hot-spot maps of TB and unsuccessful treatment outcomes. Phase II was a prospective cohort in Hulu Langat (2018-2020) where 340 respondents were new TB cases registered in government health clinics and their data was recorded using self-reported questionnaire and standardized data collection forms. Kaplan-Meier survival analysis with Log rank test was used to estimate the time to unsuccessful treatment outcomes and Cox proportional hazard model was used to calculate the hazard ratios of unsuccessful treatment outcomes at 95% confidence interval and level of significance set at 0.05. Unsuccessful treatment outcomes in Selangor were 25.1% with highest proportion being loss to follow-up (11%) and death (9.1%). Spatio-temporal clusters and hotspots of TB incidence and unsuccessful treatment outcomes varied in the study but were persistent in 5 sub-districts (Sungai Buloh, Damansara, Petaling, Ampang and Cheras). Risk factors of unsuccessful treatment outcomes in Selangor included male, age >35yrs, Non-Malaysians, urban area, unemployed, history of incarceration, smokers, human immunodeficiency virus (HIV) positive status, pulmonary tuberculosis, retreatment case, advanced chest x-ray, positive sputum at 2nd month of treatment, multi-drug resistant tuberculosis (MDR-TB), public hospital/ clinic as place of starting treatment, shorter duration of treatment and

unsupervised directly observed therapy (DOT). Unsuccessful treatment outcomes in Hulu Langat were 20.0% with highest proportions being not evaluated (10.9%) and loss to follow-up (7.4%). Mean survival time to unsuccessful treatment outcome was 7.6 months with 80.0% occurring in the first 3 months of treatment. Risk factors of hazard probability of unsuccessful treatment outcomes in Hulu Langat were male, underweight, Malay ethnicity, cigarette/vaping, not done sputum at 2nd month of treatment and public mode of transport.

Unsuccessful treatment outcomes in Selangor were high in certain districts and sub-districts. Hotspots of TB incidence and unsuccessful treatment outcomes clustered in the central region of Selangor. Strengthening of the existing TB control programs especially in the central eastern and western sub-districts is recommended. Programs aimed to reduce loss to follow-up and death needed within the first three months of treatment in Selangor. Engaging community/non-governmental organization (NGO) in TB management and DOT especially for Non-Malaysian and incarcerated TB patients. Integrating vaping de-addiction in the existing smoking cessation programs at the health clinic levels and providing free public transport to reach the health centers are recommended.

Keywords: tuberculosis, unsuccessful treatment outcomes, GIS, survival, Malaysia

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah.

## **TREND SPATIOTEMPORAL DAN FAKTOR-FAKTOR RISIKO HASIL RAWATAN YANG TIDAK BERJAYA DI PESAKIT TUBERKULOSIS DI SELANGOR, MALAYSIA.**

Oleh

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Tuberkulosis (TB) tetap menjadi penyebab utama kematian antara penyakit berjangkit di Selangor, Malaysia. Untuk mengenal pasti trend spatio-temporal dan faktor risiko hasil rawatan yang tidak berjaya dan menentukan ramalan dan masa ke hasil rawatan yang tidak berjaya di Selangor, Malaysia. Fasa I ialah kohort retrospektif di Selangor (2014-2017) di mana 18136 responden daripada daftar TB telah dipilih dan data mereka direkodkan menggunakan borang pengumpulan data standard dan kemudian dianalisis menggunakan SPSS versi 25.0 (multiple logistic regression) untuk mengenal pasti faktor risiko yang tidak berjaya hasil rawatan (mati, terhenti rawatan, gagal rawatan, dan pindah, keluar dan hilang) dan ArcGIS versi 10.4 (Statistik global Moran I dan Getis dan Ord (Gi\*)) untuk menganalisis taburan spatial, pengelompokan spatio-temporal dan membangunkan peta dan rawatan tempat liputan TB hasil tidak berjaya. Fasa II merupakan kohort prospektif di Hulu Langat (2018-2020) di mana 340 responden adalah kes TB baharu yang didaftarkan di klinik kesihatan kerajaan dan data mereka direkodkan menggunakan soal selidik yang dilaporkan sendiri dan borang pengumpulan data standard. Analisis survival Kaplan-Meier dengan Log rank test digunakan untuk menganggarkan masa untuk hasil rawatan yang tidak berjaya dan Cox proportional hazard model digunakan untuk mengira nisbah bahaya hasil rawatan yang tidak berjaya pada selang keyakinan 95% dan tahap keertian ditetapkan pada 0.05. Hasil rawatan yang tidak berjaya di Selangor adalah 25.1% dengan perkadaran tertinggi ialah terhenti rawatan (11%) dan kematian (9.1%). Kelompok spatio-temporal dan titik panas kejadian TB dan hasil rawatan yang tidak berjaya berbeza-beza dalam tempoh kajian tetapi berterusan di 5 mukim (Sungai Buloh, Damansara, Petaling, Ampang dan Cheras). Faktor risiko hasil rawatan yang tidak berjaya di Selangor termasuk lelaki, umur >35 tahun, bukan warganegara Malaysia, kawasan bandar, menganggur, sejarah peminjaraan, perokok, status positif human immunodeficiency virus (HIV), tuberkulosis paru-paru, kes rawatan semula, x-ray dada lanjutan, kahak positif pada bulan ke-2 rawatan, tibi tahan pelbagai

ubat (MDR-TB), hospital/klinik awam sebagai tempat memulakan rawatan, tempoh rawatan yang lebih singkat dan terapi pemerhatian terus tanpa pengawasan (DOT). Hasil rawatan yang tidak berjaya di Hulu Langat adalah 20.0% dengan perkadaran tertinggi pindah, keluar dan hilang (10.9%) dan terhenti rawatan (7.4%). Purata masa hidup hingga hasil rawatan yang tidak berjaya ialah 7.6 bulan dengan 80.0% berlaku dalam 3 bulan pertama rawatan. Faktor risiko kebarangkalian bahaya hasil rawatan yang tidak berjaya di Hulu Langat adalah lelaki, kurang berat badan, etnik Melayu, rokok/vaping, tidak melakukan kahak pada bulan ke-2 rawatan dan pengangkutan awam.

Hasil rawatan yang tidak berjaya di Selangor adalah tinggi di daerah dan mukim tertentu. Titik panas kejadian TB dan hasil rawatan yang tidak berjaya berkumpul di kawasan tengah Selangor. Pengukuhan program kawalan TB sedia ada terutamanya di mukim timur tengah dan barat adalah disyorkan. Program bertujuan untuk mengurangkan terhenti rawatan dan kematian yang diperlukan dalam tempoh tiga bulan pertama rawatan di Selangor. Melibatkan komuniti/pertubuhan bukan kerajaan (NGO) dalam pengurusan TB dan DOT khususnya untuk pesakit TB bukan warganegara Malaysia dan dipenjara. Mengintegrasikan nyahketagihan vape dalam program berhenti merokok sedia ada di peringkat klinik kesihatan dan menyediakan pengangkutan awam percuma untuk sampai ke pusat kesihatan adalah disyorkan.

Kata kunci: tuberkulosis, hasil rawatan yang tidak berjaya, GIS, kelangusan hidup, Malaysia

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I certify that a Thesis Examination Committee has met on 27 August 2021 to conduct the final examination of Kaur Kirandeeep Kulwant on her thesis entitled "Spatiotemporal trends and risk factors of unsuccessful treatment outcomes among tuberculosis patients in Selangor, Malaysia" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the degree of Doctor of Philosophy.

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## LIST OF ABBREVIATIONS

ART	Anti-retroviral treatment
CI	Confidence interval
CXR	Chest X-ray
DM	Diabetes Mellitus
DOT	Directly Observed Treatment/ Therapy
DOTS	Directly Observed Treatment/ Therapy, Short Course
EPTB	Extra-pulmonary tuberculosis
GIS	Geographic Information System
Gi	Getis Ord Statistics
HIV	Human Immunodeficiency Virus
JKNS	Selangor State Health Department
LBTI	Latent TB Infection
MoH	Ministry of Health, Malaysia
MDR-TB	Multidrug-resistant tuberculosis
PKD	District Health Department
PTB	Pulmonary Tuberculosis
RR-TB	Rifampicin-resistant tuberculosis
SMR	Standard Morbidity Ratio
SLIR	Stochastic Susceptible-Latently Infected-Infectious-Recovered
SIR	Stochastic Susceptible-Infective-Recovered
TB	Tuberculosis
TBIS	Tuberculosis Information System
WHO	World Health Organization

## CHAPTER 1

### INTRODUCTION

#### 1.1 Background

Tuberculosis (TB) is a chronic airborne infectious disease which is caused by *Mycobacterium tuberculosis* and despite being a curable and preventable disease remains a public health concern (World Health Organization [WHO], 2020a). One of the main causes of death from a single infectious disease among adults globally continues to be TB since 2015 (WHO, 2020a). One new case of TB is reported every 4 seconds and more than 2 people suffering from TB die every minute in the world (Heemskerk, Caws, Marais, & Farrar, 2015). In 2019, there were 10 million TB cases reported and the highest proportion of TB cases were in South-East Asia (44%), followed by South Africa (25%) and Western Pacific (18%). TB treatment has managed to avert 60 million deaths since the year 2000 (WHO, 2020a).

The guidelines for TB control were published first by WHO in 1994 where the TB treatment outcomes were first defined as “cured, completed treatment, died, failure, defaulted, transferred out” (WHO, 1994). These were subsequently reclassified by WHO and the International Union Against Tuberculosis and Lung Disease (IUALTD) into successful treatment outcomes (cured and completed treatment) and unsuccessful treatment outcomes (default; transferred out; treatment failure; death) (WHO, 2002; Ditah et al., 2008). The treatment outcomes were revised based on their drug-susceptibility test and terms like “*default*” and “*transferred out*” were replaced by “*loss to follow-up*” and “*not evaluated*” respectively in the year 2013 with advent of new diagnostics tools and increase in the multidrug-resistant tuberculosis (MDR-TB) cases globally (WHO, 2013). The terms of treatment outcomes were last revised in 2020 to incorporate the results of WHO-approved rapid diagnostics (WRD), less judgmental language (“*defaulter*” and “*TB suspect*” replaced with “*lost to follow-up*” and “*presumptive TB*”) and improve the treatment outcome definition of *cured* and *treatment failed* for multidrug-resistant TB cohorts (WHO, 2020c). However, Malaysia follows the definitions and terms of treatment outcomes based on 2010 guidelines of WHO (Ministry of Health, Malaysia [MoH], 2012) and treatment guidelines for drug-resistant tuberculosis in line with WHO definitions were issued only in 2016 (MoH, 2016a). Standard definitions of key terms recorded by national TB programme (NTP) information systems must be used for data to be comparable within and between NTPs. Therefore, the terms and definitions used in this thesis are in line with last updated WHO definitions and reporting framework of TB of 2020 to make the results comparable not only within Malaysia but also with regions outside Malaysia and the term unsuccessful treatment outcome used in this research includes *died*, *failure*, *loss to follow-up* and *not evaluated* (WHO, 2020c).

Standardized process of treatment outcome monitoring is important for countries as it allows systematic evaluation of the effectiveness of the national TB control program (NTP) (Manissero, Hollo, Huitric, Ködmön, & Amato-Gauci, 2010). Of the three strategies launched by WHO to combat TB the most popular '*Directly Observed Therapy Short Course*' or better known as DOTS has been adopted by many countries (WHO, 1995). One of the five key components of this strategy included a monitoring system for program supervision and evaluation (WHO, 1999; WHO, 2006). The Stop TB strategy launched next was designed to achieve the Millennium Development Goal (MDG) 6 (Target 8) to have halted and reverse the incidence of TB by 2015 (WHO, 2006). The End TB strategy was launched by WHO in 2014 to achieve the United Nations Sustainable Development Goal 6 which was to end the TB epidemic (WHO, 2015). The milestone of End TB strategy was reduction in the TB incidence rate and TB mortality rate by 20% and 35% respectively, in 2020 compared to 2015 (WHO, 2014a).

Globally, the End TB strategy milestone was not achieved as the TB incidence and TB mortality worldwide reduced only by 9% and 14% respectively between 2015 and 2019. However, WHO European Region and seven high TB burden countries achieved the target of 20% and 35% reduction in TB incidence and TB deaths by 2020 compared to 2015 as baseline. The overall unsuccessful treatment outcomes (death, treatment failure, loss to follow up, not evaluated) accounted for only 15% in 2019. (WHO, 2020a). Globally, the treatment success was of 85% in 2018 with highest being in WHO Eastern Mediterranean Region (91%) closely followed by WHO Western Pacific Region (89%) and lowest in the WHO European Region (76%) and WHO Region of Americas (76%). Of the estimated 10 million people who developed TB in 2019, 1.2 million [among the human immunodeficiency virus (HIV)-negative] and 208 thousand (among the HIV-positive) died. Treatment failure was highest in the WHO European Region (11%), death was highest in WHO South-East Asia Region (17%), loss to follow up was highest in the WHO Western Pacific Region (26%) and not evaluated was same for all the WHO regions of 4-6% in the 2017 cohort (WHO, 2020a).

The WHO Western Pacific Region (WPRO) accounted for 18% of the global TB burden in 2019 with TB incidence rate of 93 per 100 000 populations and TB mortality rate (among HIV-negative) of 4.4 per 100 000 populations (WHO, 2020b). In 2019, of the 37 countries and areas in the WPRO, eleven countries were categorized as high TB burden countries (WHO, 2020a). China along with Philippines of the WPRO together accounted for 80% of the total TB cases with 866000 (47%) and 591000 (32%) in 2018 (Morishita, et al., 2020). The prevalence of unsuccessful treatment outcomes for WPRO was 11% in 2019 (WHO, 2020b). WPRO, has achieved two out of three milestones of the End TB strategy namely, reduction in TB incidence rate compared to 2015 by 20% and also TB treatment success rate of more than 80%. The third milestone of reduction in number of TB deaths by 35% compared to 2015 was not achieved by WPRO as it was 30% in 2019 (WHO, 2020a). Although, Malaysia was not in the top ten countries list of high TB incidence rates in the WPRO but it ranked as the 9th country with highest MDR /RR-TB cases of 480 in 2018 (Morishita et al., 2020).

Malaysia is currently categorized as an Intermediate TB burden country by WHO with TB incidence rate of 92/100 000 population, TB mortality rate (among HIV-negative) of 3.8/ 100 000 population and treatment success rate of 79% in 2019 (WHO, 2020b). TB has remained the leading cause of death in Malaysia from an infectious disease for more than a decade (MoH, 2020a; MoH, 2010). Malaysia is far from achieving the End TB strategy milestones of 2020 with only 2.4% reduction in the TB incidence rate (2015-2019) and increment of 36.8% in the number of TB deaths as opposed to the target of 20% and 35% reduction by 2020 respectively. In addition to this, Malaysia is under constant threat as it is surrounded by neighbouring countries (Thailand, Indonesia, Vietnam, Cambodia and Philippines) which are declared as high TB burden countries by WHO (WHO, 2020b). Among the various strategies adopted by Malaysia to combat TB are: launch of Malaysia National Tuberculosis Control Programme (NTBCP) and BCG vaccination, guidelines for chemotherapy of TB, DOTS, integration of the National TB Program (NTP) into the general medical and health system, Isoniazid prophylaxis therapy (IPT), mandatory TB screening of foreign workers, screening of TB in prisons and drug rehabilitation centers, national electronic web-based TB registry (myTB), use of fixed dose combination (FDC), National Strategic Planning for TB Management and Control (NSPTB) (NSPTB 2011-2015 and NSPTB 2016-2020), screening high risk groups for TB and monetary incentives to increase adherence to treatment (MoH, 2016c, MoH, 2015, MoH, 2012). One out of every five TB patients had unsuccessful treatment outcome in Malaysia (Liew et al., 2015; Tok et al., 2020).

The TB transmission pattern is influenced by geographic and social factors therefore geographic information system (GIS) has become an important tool in identifying high-risk populations and geographic areas of TB (Beiranvand et al., 2016). New tools of epidemiology surveillance such as mapping of diseases especially TB has been put in place by many developed countries. Of late, the use of geographic information system (GIS) and spatio-temporal statistical analyses have become indispensable in identification of areas with ongoing disease transmission (Gomez-Barroso, Rodriguez-Valin, Ramis, & Cano, 2013). GIS applications in the health informatics and epidemiology include profiling of community health, disease surveillance, disease mapping, health risk analysis, health access and planning. Geoprocessing techniques can contribute to the existing epidemiological surveillance (Pinto et al., 2015). Understanding spatial patterns is important for health managers to plan effective TB control methods (Beiranvand et al., 2016). GIS has been deployed in many countries currently to assess the spatial distribution of and clustering of TB (De Vries et al., 2014; Sun et al., 2015; Dangisso, Datiko, & Lindtjorn, 2015; Das & Horton, 2015; Ge, Zhang, Wang, & Wei, 2016; Mahara, Yang, Chen, Wang & Guo, 2018; Hasker et al., 2020; Liao, Ju, Gao, & Pan, 2020).

The factors influencing the unsuccessful TB treatment outcomes can be broadly classified into patient factors, disease factors and treatment factors. The patient factors can be further divided into sociodemographic factors, co-morbidities and lifestyle, which are significantly, associated with unsuccessful treatment outcomes. The sociodemographic factors such as male gender (Mohammadien, Alkhatay, Hamed, & Shaaban, 2017; Vasankari, Holmström, Ollgren, Liippo, &

Ruutu, 2010); elderly age (Oshi, Oshi, Alobu & Ukwaja, 2014; Vasankari et al., 2010); immigrant status/ foreigner (Atif et al., 2014a; Liew et al., 2015); low level of education/ illiteracy (Atif et al., 2014; Liew et al., 2015; Nafae, Elshahat, Said & Ibrahim, 2017;); urban slum residents (Gadoev et al., 2015; Snyder, Marlow, Phuphanich, Riley, & Maciel, 2016) were noted to be associated with unsuccessful treatment outcomes among tuberculosis patients. The comorbidities such as HIV (Biruk, Yimam, Abrha, Biruk & Amdie, 2016; Garcia-Basteiro et al., 2016; Oshi, et., 2014); diabetes (Chaudhry, Ba Essa, Al-Solaiman, & Al-Sindi, 2012; Reis-Santos et al., 2014; Siddiqui, Khayyam, & Sharma, 2016); immunosuppression (Vasankari et al., 2010) were reported to be associated with unsuccessful treatment outcomes in tuberculosis patients in various literatures.

The TB patients with history of smoking (Gegia et al., 2015; Liew et al., 2015), history of incarceration (Gegia et al., 2015) and without jobs (Gadoev et al., 2015) were noted to have higher rates of unsuccessful treatment outcomes. Among the disease factors extra-pulmonary TB (EPTB) (Biruk et al., 2016; Oshi, et., 2014;); advanced CXR lesion (Nafae et al., 2017); presence of lung cavities at start of treatment (Atif et al., 2014a) were all found to be associated with unsuccessful treatment outcomes. The treatment factors such as history of previous treatment (Ananthakrishnan, et al., 2013; Biruk et al., 2016; Sengul et al., 2015); history of treatment failure (Gafar, Nyazema, & Dambisya, 2014; Reis-Santos et al., 2014); positive AFB smear score at two months after treatment (Dooley, et al., 2011; Siddiqui, et al., 2016), initial sputum smear for AFB testing positive (Biruk et al., 2016; Gegia et al., 2015); drug-resistant status (Atif et al., 2017; Gegia et al., 2015; Sengul et al., 2015); history of treatment interruption (Biruk et al., 2016; Dooley et al., 2011; Nahid et al., 2011); high grade AFB sputum (Atif et al., 2014a) were all reported to have unsuccessful treatment outcomes in the literatures. The screening for diabetes mellitus (DM) in all people diagnosed with TB and screening for TB in people with DM has been recommended in the collaborative framework for care and control of TB and diabetes by IULTD and WHO in 2011 (WHO, 2011).

The spatial pattern of TB is influenced by population density (Dangisso et al., 2015; Mahara et al., 2018), urban areas (Rodrigues et al., 2017; Masabarakiza & Hassan, 2019) and income status (Pinto et al., 2015; Rasam et al., 2018). Urbanization in Malaysia has created high density housing areas like rumah kongsi (a shared makeshift house which is shared by many construction site workers in Malaysia), squatters and high-rise flats which are susceptible to TB contagions because of their poor ventilation; created new places of high public concentration such as shopping complexes, public transport terminals, public buildings, educational places and public recreational places which can be easily visited by the infected individuals as they appear just as healthy as everyone else and also the practice of use of nose mask in public places is still not common in Malaysian society. Lastly, urbanization has attracted of foreigners from high burden TB countries for study/ work or leisure purpose and thereby putting the local population at risk of contracting TB (Mokhtar & Rahman, 2017). There is an increase in international travel and migrant populations from high burden TB countries in Malaysia. In 2013, thirty-three deaths related to TB were recorded per week in Malaysia.

Two national level studies have reported that one out of every 5 TB patients had unsuccessful treatment outcome (Liew et al., 2015; Tok et al., 2020). To date, a few studies from different states of Malaysia have reported treatment outcomes of tuberculosis patients with a very high heterogeneity in the results (Atif et al., 2014a; Atif et al., 2017; Ismail & Bulgiba, 2013; Liew et al., 2015) but neither of them have reported on the spatio-temporal trends of tuberculosis, nor have they reported on the time to unsuccessful treatment outcomes in tuberculosis patients. The knowledge of time to unsuccessful treatment outcomes in tuberculosis patients is important for the timely deployment of interventions to reduce the proportion of unsuccessful treatment outcomes among TB patients in the region. The words unsuccessful, unfavourable, adverse and poor treatment outcomes have been used interchangeably in the literature (Mundra, Deshmukh & Dawale, 2017; Garcia-Basteiro et al., 2016; Sengul et al., 2015; Atif et al., 2014a; Choi et al., 2014; Ananthakrishnan et al., 2013). From this point forward, the term “unsuccessful treatment outcomes” was used in this study.

## 1.2 Problem Statement

At national level, Malaysia was close to achieving the 2020 milestones of End TB Strategy with TB treatment success rate of 84%, TB incidence of 81/100000 population and TB mortality rate of 3.69/100000 in 2019 (MoH, 2019a). However, at the state level of Selangor which is one of the most populous states of Malaysia these 2020 milestones were very far from the target. The TB treatment success rate was 63% for Malaysians and 36% for Non-Malaysians, TB incidence of 80/100000 population and TB mortality rate of 4.27/100000 in 2019 in Selangor (MoH, 2019a).

Selangor reported the highest number of TB cases (n=5211) and deaths (n=279) in the peninsular Malaysia in 2019 (MoH, 2020a). There was 84% (n=2382 cases) increase of tuberculosis cases from 2829 cases in 2010 to 5211 cases in 2019 in Selangor (MoH, 2010; MoH, 2020a). Tuberculosis was the third most commonly notified infectious disease with an incidence rate of 75 per 100 000 population after Dengue/ Dengue Haemorrhagic Fever (1076/100 000 population) and Hand, Foot & Mouth Disease (81/100 000 population) in 2015 in Selangor (Selangor State Health Department [JKNS], 2015; JKNS, 2018). More than 2/3<sup>rd</sup> (80% and 82%) of the TB cases in Selangor in 2015 and 2018 were of pulmonary TB (PTB) type (JKNS, 2015; JKNS, 2018), which puts the population of Selangor at greater risk of contracting TB as it is the sputum positive pulmonary TB patients that are responsible for spreading the infection in the droplets of their cough/ sneeze (Shanmuganathan & Shanmuganathan, 2015). The number of paediatric TB cases in Selangor increased by 28% (n=31) from 112 cases in 2013 to 143 cases in 2018 with majority of the children being Malaysian (93%). This reflects ongoing transmission within communities in Selangor. Tuberculosis among the foreigners in Selangor was only 15% compared to Malaysian citizens (85%) in the year 2018. More than half (69%) of these foreigners were from two high-TB burden countries Indonesia (40%) and Myanmar (29%). There is an increase of 474 deaths due to TB in Selangor from 111 in 2010 to 575 in 2018 (JKNS, 2011; JKNS, 2018).

The TB lost to follow-up rate increased sharply from 2.0 (2010) to 15.0 (2015) whereas the MDR-TB cases increased only by 4 cases between 2014 and 2015 (Ramli, 2017). Among the 9 districts of Selangor, Hulu Langat and Gombak had the highest incidence rates of 94 and 93 per 100 000 population respectively surpassing even the National incidence rate of 79.45 in 2015 (JKNS, 2015). The TB incident rate in Hulu Langat district showed a 53% increase from 61.8 per 100 000 population in 2011 (JKNS, 2011) to 94 per 100 000 population in 2015 (JKNS, 2015). Despite all the efforts of the government, Selangor has not been able to achieve the cure rate of  $\geq 85\%$  rates which calls for a need to analyse the contributing factors and if possible, predictors of unsuccessful treatment outcomes of TB.

Among the studies published on TB treatment outcomes in Malaysia, most were either at national level (Liew et al., 2015; Tok et al., 2020) or conducted in other states or cities (Zulkipli, Mohd Salleh & Ahmed, 2018; Khan, Sulaiman, Muttalif, Hassali, Aftab & Khan, 2019; Tok, Salvaraji, Rosli & Badrul, 2016; Nik, Mohd, Wan, Sharina & Nik, 2011). The studies on TB conducted in Malaysia have explored latent-tuberculosis infection TB (LTBI), multi-drug resistant tuberculosis (MDR-TB) (Shariff, Shah & Kamaludin, 2016a; Shariff, Shah & Kamaludin, 2016a), pulmonary tuberculosis (PTB) (Tok et al., 2016; and TB-HIV co-infection (Jalal, Abdullah, Abd Wahab, Dir & Naing, 2017; Ismail & Bulgiba, 2013). Since the routinely collected TB surveillance data lacked information on certain risk factors a prospective study design was incorporated in this research as Phase II where additional known risk factors were included such as weight, height, monthly income, duration of the comorbidities such as diabetes, details about lifestyle factors such as smoking, alcohol consumption habits and distance from the treatment centre. The spatial patterns of TB have been explored in Malaysia (Diah, Aziz & Ahmad, 2016a; Diah et al., 2016b; Diah et al., 2017a; Rasam et al., 2017; Rasam et al., 2018) but not of unsuccessful treatment outcomes. There is also a scarcity of literature on spatio-temporal trends and prospective study designs on time to unsuccessful treatment outcomes of tuberculosis in Selangor.

### **1.3 Significance of the study**

The spatial distribution of TB is non-random and clustered according to many studies. This study aimed to provide maps of spatial distribution of TB incident cases and unsuccessful treatment outcomes in Selangor which had not been reported in the literature before. The standardized maps based on TB incident cases provided more robust evidence of the TB burden in Selangor. The use of sub-district as the geographical unit gave a better understanding of the regional TB burden. This study also identified the high-risk areas (hotspots and clusters) of TB incidence and unsuccessful TB treatment outcomes for Selangor state based on geostatistical analysis. This knowledge can be utilized by public health authorities to strengthen regional TB prevention and control strategies including targeted screening among high-risk groups, contact investigations and integration of NGOs/community in the TB management especially for DOTS supervision and transportation facilities to health centres. Control efforts are best designed when the areas of high incidence are known. The prospective cohort

study design confirmed the observations of previous retrospective studies done in Malaysia and also identified the risk factors and time to unfavorable treatment outcomes. The identification of the risk factors of and time to unsuccessful treatment outcomes can not only help in recognition of patients at risk but also allow the development of timely adjunctive treatment strategies. Assessment of treatment outcomes helps the State and District TB managers to gauge the effectiveness of their existing tuberculosis control programs. The findings of this study filled in the gap of knowledge about tuberculosis at sub-district level in the state of Selangor and also in particularly the Hulu Langat district. Treatment outcomes and trends evaluated at the district, and sub-district levels, along with national levels identify high-performing districts or units and provide positive feedback to employees, allowing successful strategies to be repeated elsewhere. This study was the first to provide an insight on the risk factors influencing the unsuccessful TB treatment outcomes in Selangor and Hulu Langat. The retrospective (Phase I) study design provided information on risk factors of unsuccessful TB treatment outcomes at state level while the prospective (Phase II) study design provided the same information along with time factor but at sub-district (mukim) level. This study revealed if the risk factors at state and sub-district level were the same for unsuccessful TB treatment outcomes.

#### **1.4 Research Questions**

This study was conducted in two Phases.

The research questions for Phase I are as follows:

1. What is the distribution of TB cases and unsuccessful TB treatment outcome cases in Selangor, Malaysia (2014-2017)?
2. Which are the hot spot areas of TB and unsuccessful TB treatment outcomes in Selangor, Malaysia (2014-2017)?
3. What are the risk factors of unsuccessful tuberculosis treatment outcomes in Selangor, Malaysia (2014-2017)?

The research questions for Phase II are as follows:

4. What is the time to unsuccessful TB treatment outcomes in Hulu Langat, Selangor, Malaysia (2018-2019)?
5. What are the risk factors of hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Selangor, Malaysia (2018-2019)?



## **1.5 Research Objectives**

### **1.5.1 General Objective**

To identify in Phase I, the spatiotemporal trends and associated factors of unsuccessful treatment outcomes (2014-2017) in Selangor and in Phase II, determine the risk factors and time to unsuccessful treatment outcomes among tuberculosis patients (2018-2020) in Hulu Langat District.

### **1.5.2 Specific Objectives**

The specific objectives for Phase I are as follows:

1. To identify the characteristics of the TB cases by:
  - a. Patient factors (gender, age, ethnicity, nationality, residential area, education level, employment status, occupation type, comorbidities, smoking, history of incarceration,)
  - b. Disease factors (type of TB, category of TB case, chest x-ray grading, drug resistant status, sputum AFB status, AFB smear score,)
  - c. Treatment factors (place of diagnosis, place of starting treatment, DOT supervision, duration of treatment)
2. To determine the spatial and temporal trends of TB cases and unsuccessful TB treatment outcomes in Selangor, Malaysia (2014-2017).
3. To develop the hotspot map of TB and unsuccessful TB treatment outcomes in Selangor, Malaysia (2014-2017).
4. To determine the predictors of unsuccessful TB treatment outcomes in Selangor, Malaysia (2014-2017).

The specific objectives for Phase II are as follows:

1. To identify the time to unsuccessful TB treatment outcomes in Hulu Langat, Selangor, Malaysia (2018-2019).
2. To determine the association between patient factors, disease factors and treatment factors with hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Selangor, Malaysia (2018-2019).
3. To identify the risk factors of hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Selangor, Malaysia (2018-2019).

## **1.6 Research Hypotheses**

The research hypotheses for Phase I are as follows:

H<sub>1</sub>: The male patients have higher than females the probability of unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>2</sub>: The elderly patients have higher than younger patients the probability of developing unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>3</sub>: The Non- Malaysian patients have higher than Malaysian patients the probability of developing unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>4</sub>: The illiterate patients have higher than the educated patients the probability of developing unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>5</sub>: The urban patients have higher than the rural patients the probability of developing unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>6</sub>: The jobless patients have higher than the patients with jobs the probability of developing unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>7</sub>: The patients with comorbidities have higher than the patients without comorbidities the probability of unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>8</sub>: The smoking patients have higher than the non-smoking patients the probability of developing unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>9</sub>: The patients with history of incarceration have higher than the patients with no history of incarceration the probability of unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>10</sub>: The patients with pulmonary tuberculosis have higher than the patients with extra-pulmonary tuberculosis the probability of unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>11</sub>: The patients with advanced chest x-ray grading have higher than the minimal chest x-ray grading the probability of unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>12</sub>: The patients with drug resistant TB have higher than the patients with drug susceptible TB the probability of unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>13</sub>: The patients with positive sputum AFB at second month of treatment have higher than the patients with negative sputum AFB at second month of treatment the probability of unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>14</sub>: The patients with high grade sputum AFB smear score have higher than the patients with low grade sputum AFB smear score the probability of unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>15</sub>: The patients in the category of retreatment case have higher than the patients in the category of new case the probability of unsuccessful TB treatment outcomes in Selangor, Malaysia.

H<sub>16</sub>: The patients having hospital as their place of starting treatment have higher than the patients having clinic as their place of starting treatment the probability of unsuccessful TB treatment outcomes in Selangor, Malaysia.

The research hypotheses for Phase II are as follows:

H1: The male patients have higher than females the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H2: The elderly patients have higher than younger patients the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H3: The Non- Malaysian patients have higher than Malaysian patients the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H4: The illiterate patients have higher than the educated patients the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H5: The urban patients have higher than the rural patients the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H6: The jobless patients have higher than the patients with jobs the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H7: The patients with comorbidities have higher than the patients without comorbidities the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H8: The smoking patients have higher than the non-smoking patients the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H9: The patients with history of incarceration have higher than the patients with no history of incarceration the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H10: The patients with pulmonary tuberculosis have higher than the patients with extra-pulmonary tuberculosis the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H11: The patients with advanced chest x-ray grading have higher than the minimal chest x-ray grading the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H12: The patients with drug resistant TB have higher than the patients with drug susceptible TB the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H13: The patients with positive sputum AFB at second month of treatment have higher than the patients with negative sputum AFB at second month of treatment the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H14: The patients with high grade sputum AFB smear score have higher than the patients with low grade sputum AFB smear score the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H15: The patients in the category of retreatment case have higher than the patients in the category of new case the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

H16: The patients having hospital as their place of starting treatment have higher than the patients having clinic as their place of starting treatment the hazard probability of unsuccessful TB treatment outcomes in Hulu Langat, Malaysia.

## **1.7 Structure of Thesis**

This thesis is divided into 6 chapters. Chapter 1 is the introduction that provides the background of the research and outlines the chapters in the thesis. Chapter 2 shows the literature review of tuberculosis treatment outcomes and application of GIS in TB surveillance. It provides background to the thesis by reviewing the evidence from published literatures. Chapter 3 describes in detail the methods deployed to obtain the data for Phase I and Phase II of the study between 24<sup>th</sup> November 2018 and 1<sup>st</sup> March 2020. The data for Phase II was collected from 10 Health Clinics in Hulu Langat. Chapter 4 describes the details of GIS analysis and the distribution and hotspot maps of TB and unsuccessful TB treatment outcomes. It documents the comprehensive statistical analysis and results of factors associated with unsuccessful tuberculosis treatment outcomes for Phase I and results of factors associated with time to unsuccessful tuberculosis treatment outcomes for Phase II. Finally, it provides the predictors of unsuccessful tuberculosis treatment outcomes using multivariate logistic regression and predictors of time to unsuccessful tuberculosis treatment outcomes using Cox Proportional Hazard analysis. Chapter 5 discusses the findings of this study in comparison with other studies from developed and developing countries and highlights the implications of the findings. Chapter 6 concludes the thesis and provides recommendations for further research and suggestions for policy makers.

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